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Cancer treatment by telomerase inhibitors: predictions by a kinetic model

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Abstract

The inhibition of telomerase activity in actively dividing cells leads to shortening of their telomeres and suppression of cell growth when the telomere lengths become smaller than a certain threshold value (typically about 1–2 kb of DNA). We evaluated the time (efficacy delay) required to reach the threshold telomeric DNA size after initiation of treatment, which is of critical importance for the efficacy of telomerase inhibitors. A model based on the solution of a system of differential equations was developed to analyze the efficacy delay and dynamics of tumor growth. The efficacy delay was strongly dependent on the size distribution of telomere lengths at the treatment initiation. An increase in the heterogeneity of telomere size resulted in shortening of the delay. However, the long-term dynamics of tumors with homogeneous populations of telomeres were more significantly affected by telomerase inhibitors compared to tumors with heterogeneous size distribution of telomeres. Size distribution of telomeres and tumor doubling times are of critical importance for the dynamics of tumor growth in presence of telomerase inhibitors.

Keywords: Telomere; Telomerase inhibitors; Kinetic model

1. Introduction

Telomeres are DNA-protein complexes at the chromosome termini which play an important role for their stability. Telomeric DNA sequences are lost after each cell division if not restored by the ribonucleoprotein enzyme telomerase [1,2]. Telomerase is expressed in about 80–90% of

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human cancers [3] but not in normal tissue [4]. The inhibition of telomerase activity leads to inhibition of cells growth and induction of apoptosis in vivo and in vitro [5] so, telomerase can be considered as an attractive target for therapy of cancer or other pathogenic proliferating cells [6,7]. The specific feature of the telomerase inhibitor effect is the delay. Cells enter crisis and eventually die only after certain number of cell doublings after telomere length reaches a critical value [8]. For each cell the inhibitory time delay can be defined as $T = t_d(L - L_c)/l$, where L and L_c are telomere lengths at the time of inhibition initiation (typically from 2 to 30 kb [5,9–11]) and at crisis (about 1.5 kb, [12]), respectively; l, the telomere length decrease per each cell generation (from 15 to 100 bp/division, [11,13–16]); and t_d, the doubling time of cell. Because for tumor cells t_d varies from several days to more than several months [17] while the replicative capacity could be in the range of 20 to 100 divisions [5,7], T may range from weeks to years.

To account for the telomere heterogeneity we developed a kinetic model based on the solution of a system of differential equations and used it to analyze previously reported data for the kinetics of human tumor growth [17]. We found that the telomere heterogeneity shortens the time required to reach 10% reduction of the tumor mass relative to uninhibited growth, do not change significantly the time for 50% reduction of tumor growth, and prolongs the time needed for 90% reduction of tumor volume compared to homogeneous telomeres. The tumor growth kinetics affected the inhibitory delay time in a complex way in dependence on the kinetic constants and the telomere size distribution.

2. Theoretical model

Growing tumor consists of cells of different telomere lengths. Let us divide the whole range of the telomere lengths on I equal subintervals. So, the tumor cell population having the volume V will consist of I subpopulations having volumes $V_i (V = V_1 + V_2 + \cdots + V_I)$. For simplicity, let us assume also that all cells in ith subpopulation have the equal telomere length L_i, for all $i = 1, \ldots, I$. The equality $I = 1$ corresponds to the case of homogeneous telomere lengths distribution when all cells in whole population have the same telomere length. For heterogeneous case ($I > 1$) the following approach is used for calculating of telomere length and volume for each subpopulation. Let us assume that distribution of telomere lengths for total population is normal $N(x, L_m, L_\sigma)$ with mean L_m and standard deviation L_σ so the interval $[L_m - 2L_\sigma, L_m + 2L_\sigma]$ includes 95% of telomere lengths of whole tumor cell population. Telomere length for ith subpopulation in this case is calculated as

$$L_i = L_m - 2L_\sigma + \frac{4L_\sigma}{I-1}(i-1) = L_m - 2L_\sigma\left(1 - \frac{2(i-1)}{I-1}\right) \tag{1}$$

and volume of ith subpopulation can be calculated as a volume of cells having the telomere length in the interval $L_i \pm (2L_\sigma/I - 1)$:

$$V_i = V\left(N_C\left(L_i + \frac{2L_\sigma}{I-1}, L_m, L_\sigma\right) - N_C\left(L_i - \frac{2L_\sigma}{I-1}, L_m, L_\sigma\right)\right) \tag{2}$$

where N_C, cumulative function of normal distribution. We found that $I = 7$ represents well the heterogeneous nature of the telomere lengths distribution and all calculations were performed

with this number. While I is greater than 7 the computer simulations did not lead to any significantly different results.

The tumor growth is characterized by a kinetic equation based on the exponential, logistic or Gompertz models and the kinetic constants are the same for all I subpopulations of cells. The tumor cells divide with the rate a, which leads to an increase in tumor volume proportional to the number of cells. With each cell division the telomere length decreases by l until reaching a critical length L_c (here it was assumed that all cells have the same value of L_c). Then the cells die with a constant rate g. The differential equations describing the kinetics of tumor growth are

$$\frac{dV_i}{dt} = \begin{cases} (a-f)V_i, & L_i > L_c, \\ -gV_i, & L_i \leqslant L_c, \end{cases} \quad i = 1, \ldots, I \tag{3}$$

where f corresponds to the different models:

$$f = \begin{cases} 0, & \text{exponential model} \\ bV, & \text{logistic model} \\ b\ln V, & \text{Gompertz model} \end{cases}, \tag{4}$$

and b, the constant which relates to the factors inhibiting tumor growth other than telomerase inhibitors; V, the total tumor volume which is equal to the sum of all cell subpopulation volumes. The model assumes that cell growth loss during uninhibited cell growth is accounted by the constant b in the logistic and Gompertz model and in presence of telomerase inhibitors the cells die with a rate gV_i after their telomeres reach the critical length.

The telomere length L_i for each cell subpopulation is calculated as

$$L_i = \max\left\{L_i^0 - n_i l, L_c\right\}, \quad i = 1, \ldots, I \tag{5}$$

where L_i^0, the initial telomere lengths for ith subpopulation at the time of inhibitor application. The number of cell divisions of ith subpopulation n_i is calculated by assuming that in the absence of telomerase inhibitors the deviation of the tumor growth from the exponential model is not due to cell death but rather to slowing down the cell division. The possible increase in the rate of cell divisions due to the decrease in the tumor volume in presence of telomerase inhibitors is not taken into account. Therefore,

$$n_i = \begin{cases} \ln\left(V_i/V_i^0\right)/\ln 2, & L_i > L_c \\ \left(L_i^0 - L_c\right)/l, & L_i \leqslant L_c \end{cases}, \quad i = 1, \ldots, I, \tag{6}$$

where V_i, V_i^0, the volume of cells in ith subpopulation at time t and the initial values of it ($t = 0$), respectively. For example, for the Gompertz model in the case of homogeneous distribution of telomere lengths ($I = 1$) and when $L_i > L_c$ the expression for n is the following:

$$n = (a - b\ln V_0)(1 - e^{-bt})/(b\ln 2). \tag{7}$$

For $b = 0$ this is reduced to $n = at/\ln 2$, which corresponds to the exponential growth model. Here we assume that when inhibitor presents in cell its concentration is enough to completely block the elongation of telomere by telomerase. In this case cell the decrease of telomere length will be l for each cell division.

This set of differential equations was solved numerically by using the Scientist (MicroMath Scientific Software, Salt Lake City, UT) for $I = 7$ and the initial conditions $V_i(0) = V_i^0$. The initial

values of the cell subpopulation volumes V_i^0, corresponding to initial telomere length L_i^0, were assumed either uniform (homogeneous case):

$$L_1^0 = L_2^0 = \cdots = L_I^0 = L_{\mathrm{m}}, \quad V_1^0 = V_2^0 = \cdots = V_I^0 = \frac{V^0}{I} \tag{8}$$

or normally distributed (heterogeneous case, the telomere length and subpopulation volume in this case were calculated as described above, see (1) and (2)).

The relative tumor volume V_{R} is defined as

$$V_{\mathrm{R}} = \frac{V}{V^*}, \tag{9}$$

i.e. it is equal to the ratio of the tumor volume in presence of telomerase inhibitor V to the tumor volume when there is no inhibitor in medium V^* and

$$\frac{\mathrm{d}V^*}{\mathrm{d}t} = V^*(a-f), \quad V^*(0) = V^0. \tag{10}$$

Because $V \leqslant V^*$ for all $t \geqslant 0$ the following inequality holds: $0 < V_{\mathrm{R}} \leqslant 1$. The time point t_p corresponding to percent p of reduction in relative tumor volume (t_{10}, t_{50}, see below) is defined as

$$t_p = \underset{V_{\mathrm{R}}=p}{\arg}(V_{\mathrm{R}}). \tag{11}$$

It is easy to show that for homogeneous case t_p can be calculated as

$$t_p = \frac{L_0 - L_{\mathrm{c}}}{al} \ln 2 - \frac{\ln(1-p)}{g}, \tag{12}$$

where the first term in the right-hand side of the equation corresponds to the time which is necessary to reach telomere critical length L_{c} and the second one corresponds to the time of reduction of tumor volume by percent p.

3. Results

Schwartz [17] reported clinical data for the growth kinetics of primary lung carcinomas and analyzed them by using the exponential growth model. It has been shown that these results can be described better by the Gompertz [18] and the logistic [19] models.

Fig. 1 presents the experimental data for patient RP [17]. The least squares fit to an exponential growth curve is shown as well as the predicted tumor growth in presence of telomerase inhibitors for two types of telomere lengths distribution: homogeneous and heterogeneous (see Fig. 1 legend for details and Table 1 for parameter values). One can see that the tumor growth rate begins to decline appreciably at week 30 for the heterogeneous distribution and rather abruptly for the homogeneous distribution at week 50. The dynamics for homogeneous and heterogeneous cases of telomere lengths distributions begin to differ at 11–12 week (shown by the arrow) when the telomere length in one of subpopulations reaches the crisis value L_{c}.

Fig. 2(A) shows the changes in the relative tumor volumes V_{R} (volumes in presence of telomerase inhibitors divided by volumes when no inhibitors in medium) for the homogeneous and

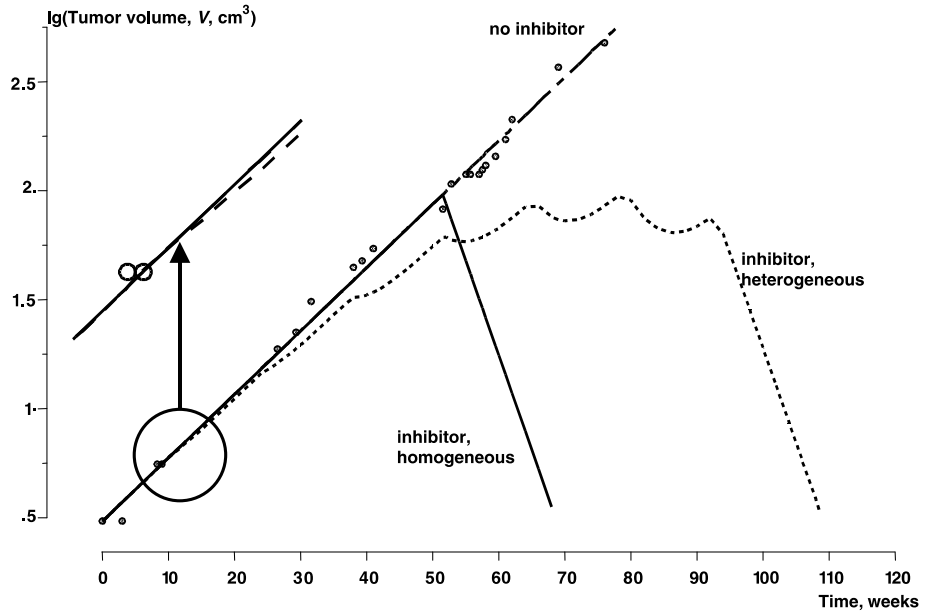

Fig. 1. Tumor volume (V, cm^3) dynamics: experimental data (○) from [17] and predicted tumor growth for exponential model in absence (– – –) or in presence of telomerase inhibitor for two types of telomere lengths distributions: homogeneous (—) and heterogeneous (- - -). Parameter values are in Table 1.

Table 1
Nomenclature of parameters

Name	Physical meaning	Value	Dimension
a	Growth rate constant	0.067	week^{-1}
b	Inhibition rate constant (for different models)	0 (exponential), 0.01 (logistic), 0.002 (Gompertz)	–
g	Apoptotic cell death rate	0.2	week^{-1}
l	Telomere length decrease rate	0.1	kb/division
L_c	Telomere length at the time of crisis	1.5	kb
L_m	Mean of telomere lengths distribution	2.0	kb
L_σ	Standard deviation of telomere lengths distribution	0.2	kb
I	Number of cell subpopulations	7	–
V^0	Initial tumor volume	3.052	cm^3

heterogeneous telomere lengths distribution in the case of exponential model. While 10% reduction in tumor volume was achieved at about 15–25 weeks after treatment for the heterogeneous distribution ($L_\sigma = 0.4$–0.2 kb, respectively), it takes longer for the homogeneous distribution (about 55 weeks) but then the effect is faster. Fig. 2(B) shows the dependence of time points t_{10} and t_{50} (corresponding to the 10 and 50% reduction in relative tumor volume, respectively) on standard deviation of telomere lengths distribution L_σ for exponential, logistic, and Gompertz model. For both models t_{50} depends weakly on L_σ, but t_{10} has quasi-linear dependence and decreases with the growth of L_σ value.

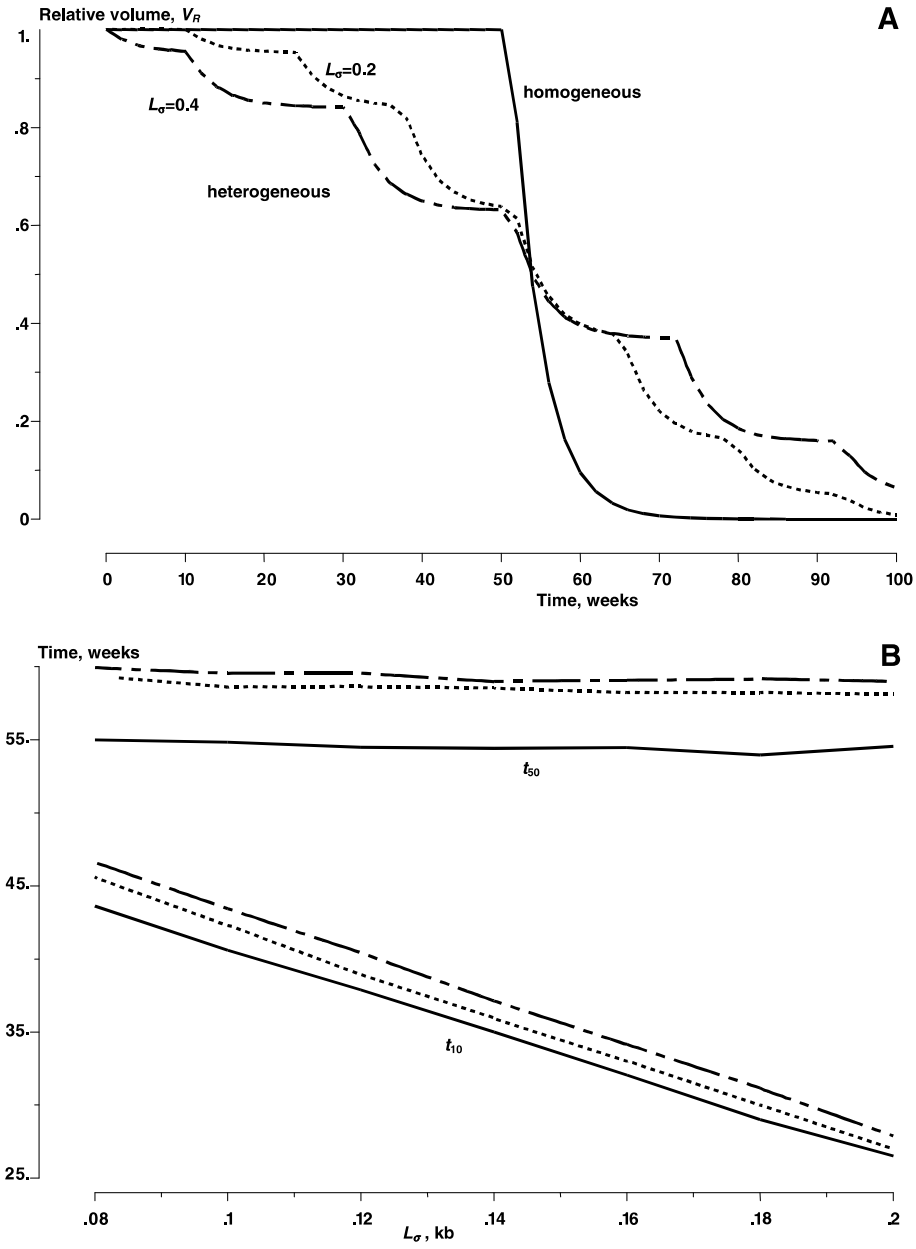

Fig. 2. (A) Changes in the relative tumor volumes V_R for the cases of homogeneous (—) and heterogeneous telomere lengths distributions for two different values of L_σ ((- - -) 0.2 kb; (– – –) 0.4 kb). (B) Dependence of t_{50} and t_{10} on standard deviation of telomere lengths distribution for three type of models: exponential (—), logistic (- - -) and Gompertz (– – –).

The telomerase inhibitor treatment leads to significant shift in the telomere lengths distribution toward shorter lengths as it is shown in Fig. 3 for 0, 20, and 40 weeks after treatment. After 80 weeks more than 60% of cells have telomere length of L_c (not shown).

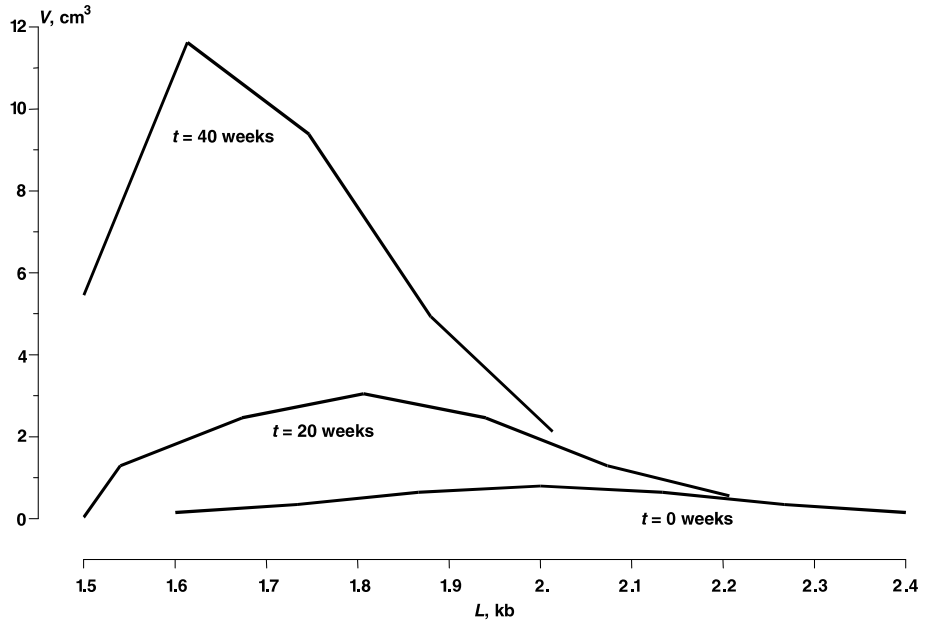

Fig. 3. Distribution of telomere lengths (L) for different time points ($t = 0$, 20, and 40 weeks) during the telomerase inhibition. It was assumed that the initial ($t = 0$) distribution of telomere lengths is normal with the parameters (kb): mean $L_{\mathrm{m}} = 2.0$ and standard deviation $L_{\sigma} = 0.2$.

The time required to reduce the tumor volume by half for both the homogeneous and the heterogeneous telomere lengths distributions was decreased from about 55 weeks to about 30 weeks (Fig. 4(A)) with the increase of telomere length shortening rate l from 0.1 to 0.2 kb/division. The values of t_{50} and t_{10} increase with the decrease of l (Fig. 4(B)), but when l is large enough these two values were changed weakly.

The increase of the death rate constant g from 0.2 to 1.0 week^{-1} (corresponding to a half-life of cells ranging from 3.5 weeks to about 5 days), however, did not have a significant effect on the inhibitory delay time (see Fig. 5(A)), it was decreased only by about 2–3 weeks. As it is shown in Fig. 5(B) the values of t_{10} and t_{50} depend weakly on g for all the models in the range of g from 0.2 to 1.0 weeks^{-1} . For smaller values of g all the models show the increase of t_{10} and t_{50} values.

We found similar qualitative features of the telomerase inhibitory effect for patients with tumor growth following the Gompertz and the logistic models. The dependence on the constant b (it accounts for the deviation from the exponential model) was affected by the method of calculating the number of cell divisions. We consider here two possibilities. Deviation from the exponential growth is due to

1. Suppression of cell division and the corresponding increase in doubling times [20] (see the formula (6) for calculation of n_i depending on V_i and V_i^0).
2. Other effects, including cell loss, and the doubling times are not changed ($n_i = at/\ln 2$, $i = 1, \ldots, I$).

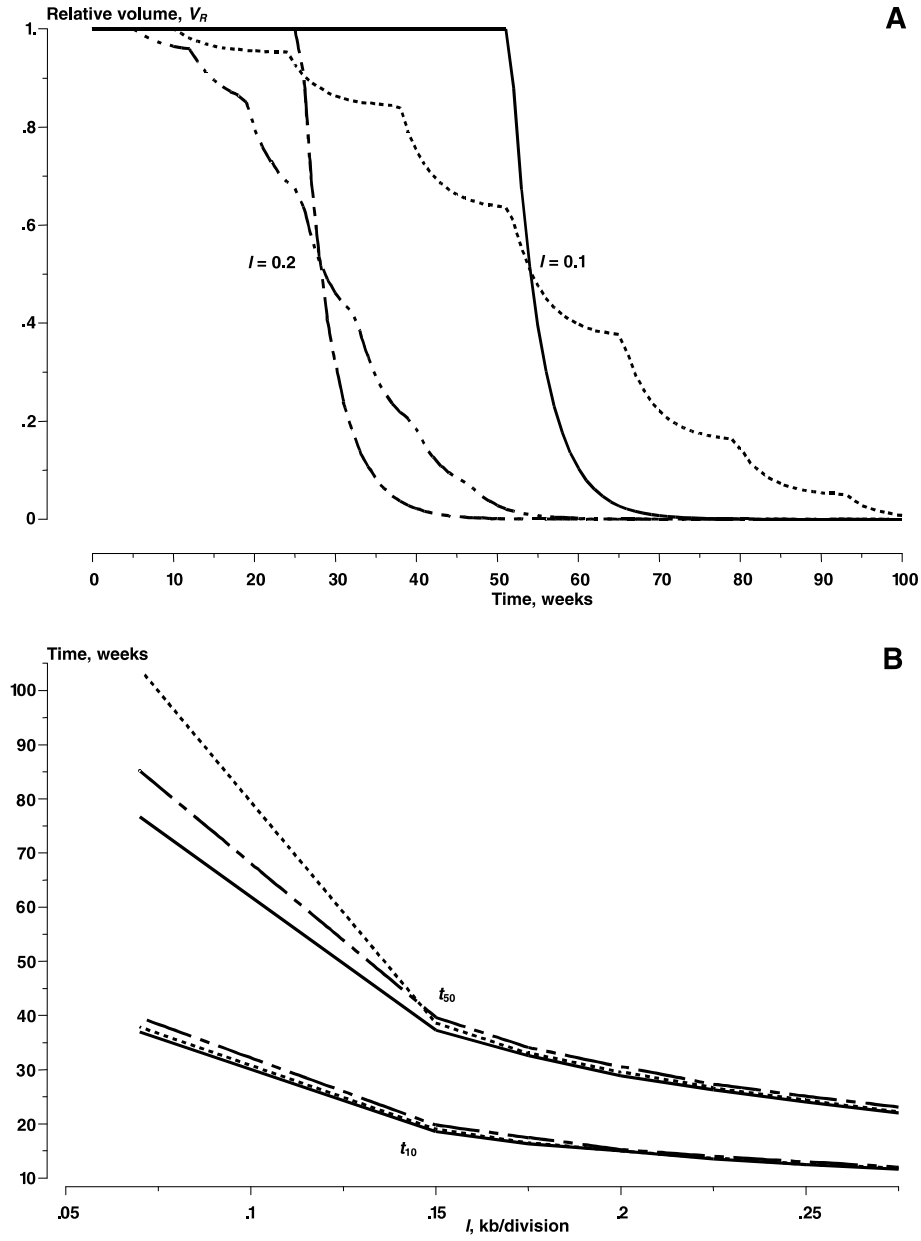

Fig. 4. (A) Changes in the relative tumor volumes for different telomere lengths distributions and telomere length decrease rates (kb/division): homogeneous, ((—) 0.1; (– - –) 0.2) and heterogeneous ((- - -) 0.1; (– – –) 0.2). (B) Dependence of t_{50} and t_{10} on telomere length decrease rate (l) for heterogeneous case of distribution and three type of models: exponential (—), logistic (- - -), and Gompertz (– - –).

Fig. 6 shows the relative volumes for these two cases calculated for different values of b (0.001, 0.02 for logistic and Gompertz model, respectively). The effect of telomerase inhibitors is significantly smaller for the first case (for both the models) compared to the second one. Further

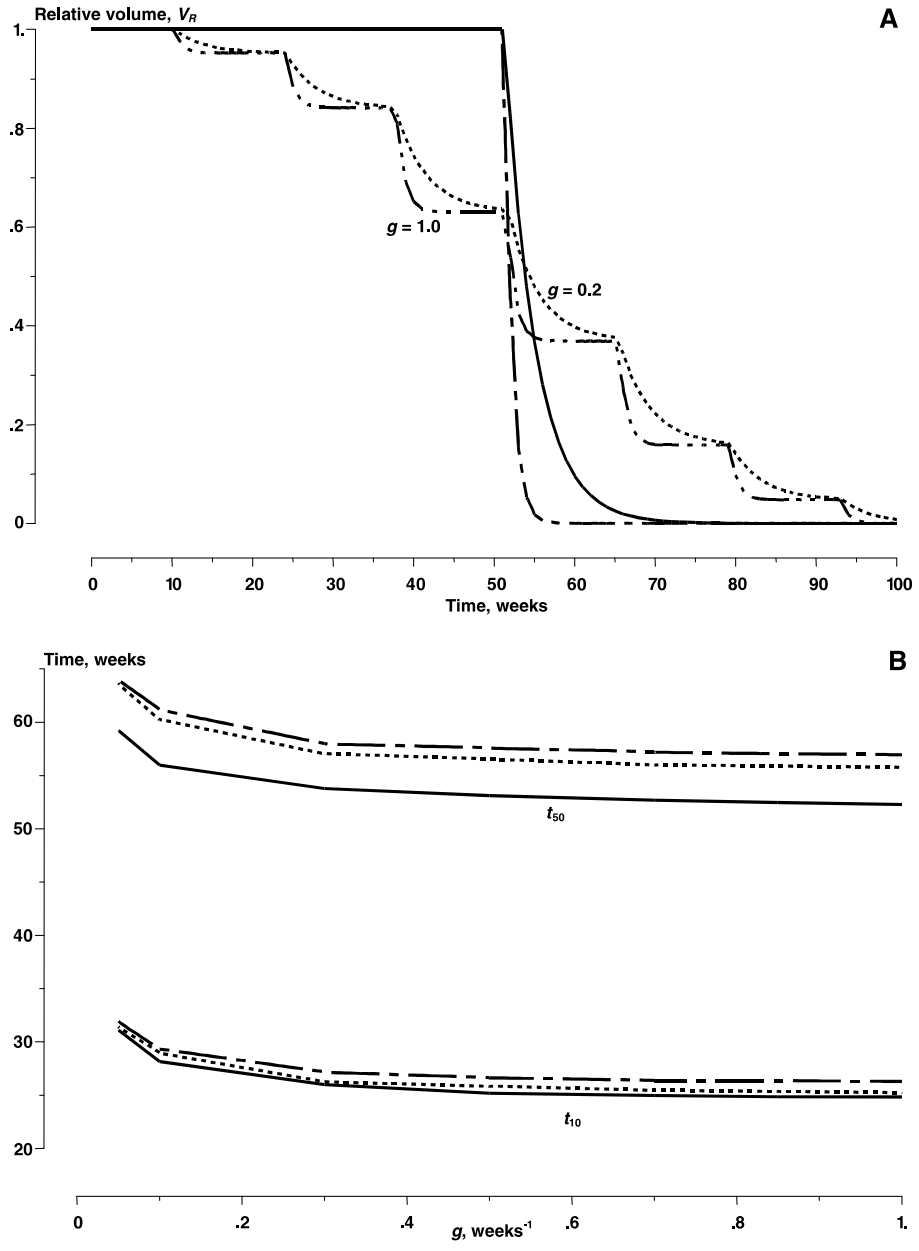

Fig. 5. (A) Effect of increase of the death rate constant from 0.2 to 1 week^{-1} for different telomere lengths distributions: homogeneous, (—) 0.2; (– - –) 1.0 and heterogeneous (- - -) 0.2; (–·–·–) 1.0. (B) Dependence of t_{50} and t_{10} on death rate constant (g) for heterogeneous telomere lengths distribution and three types of models: exponential (—), logistic (- - -), and Gompertz (– - –).

increase of b leads to lack of telomerase inhibitor effect for the first case and no significant changes for the second case (not shown).

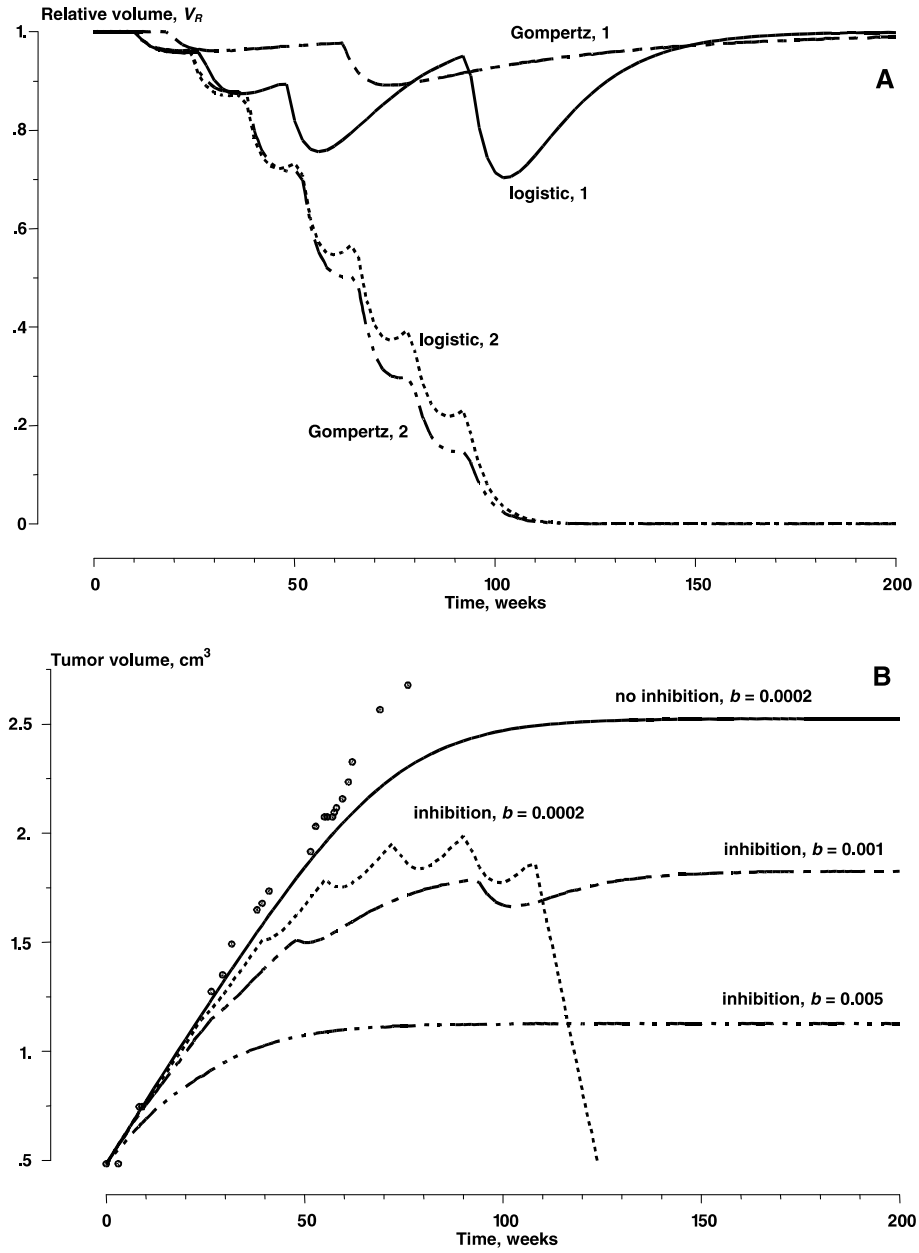

Fig. 6. (A) Relative volumes dynamics when deviation from the exponential growth depends on: (1) suppression of cell division, doubling times are increased (—) logistic model and (– - –) Gompertz model; (2) other effects, including cell loss, doubling times are not changed (- - -) logistic model and (– - - –) Gompertz model. Parameter b is equal to 0.001 and 0.02 for the logistic and Gompertz model, respectively. (B) Dynamics of tumor volume: experimental data (○) from [17] and predicted growth by the logistic model in absence (—; $b = 0.0002$) or in presence of telomerase inhibitor for three values of parameter b: (- - -) 0.0002; (– - –) 0.001 and (– - - –) 0.005. Other parameter values are in Table 1.

4. Discussion

The results presented in this paper indicate that telomerase inhibitors have the potential to decrease significantly the tumor load in a reasonable amount of time.

We investigated three types of models (exponential, logistic and Gompertz) and two types of distribution of initial telomere lengths (homogeneous and heterogeneous). It was shown that effect of telomerase inhibitors (treatments begins at $t = 0$ weeks) has a delay (Fig. 1). As one can see, the decrease of tumor volume to zero for heterogeneous distribution is dramatically delayed (later on 40 weeks) in comparison with the homogeneous one, but the initial decrease of tumor volume starts essentially earlier (after 11 weeks). For all calculations here we assumed that the telomerase inhibitor blocks completely the activity of telomerase. The partial arrest of telomerase activity can be easily described by the decreased value of the telomere length shortening per cell division ($l > 0$).

As the models predict, the time of 50% reduction of relative tumor volume (V_R) in the presence of inhibitors depends weakly on the type of model and the standard deviation of initial telomere lengths distribution. But the time of 10% reduction (as well as 90%, data not shown) has quasi-linear dependence on L_σ (Fig. 2(A) and (B)). This important feature of heterogeneous distribution model can be explained by the presence of tumor cell subpopulations having shortest and longest initial telomere length and, therefore, reaching the crisis telomere length earliest and latest, respectively. So, the more large value of the deviation of telomere length in the tumor cell population the more early effect of the decrease of tumor volume and the more delayed final recovery will be observed during the telomerase inhibitor therapy.

The average telomere lengths of tumor cells decreases with time for all subpopulations (Fig. 3) and the normal distribution (at the beginning) is changed to exponential and then to single point one (all cells have the crisis value of telomere lengths) with time. Two next figures (Figs. 4 and 5) demonstrate the dependence of model dynamics on telomere length decreases rate (l) and death rate of tumor cells (g). Tumor size decrease rate depends on type of cells (having different rates of telomere length decrease per one division and/or different programs of apoptosis) and environment/additional therapy.

Deviation from the exponential growth depends on suppression of cell division or other effects including cell loss, when doubling times increased (case 1) or not changed (case 2), respectively (Fig. 6). For the case 1 the relative tumor volume does not achieve values close to zero. For logistic function when suppression is strong ($b = 0.005$) tumor volume is stable after about 80 weeks. But for the small values of b (0.0002) tumor volume begins to decrease with time after 110 weeks. So, the decrease of the tumor cell doubling time during the telomerase inhibitor therapy can lead to the stabilization of tumor volume without final recovery. For these simulations it was assumed that parameter b has the same values in presence and absence of inhibitor, so inhibitor has no toxic or growth-stimulating effect on tumor cells.

In addition to this patient we have also examined several other patients as reported in [17] and reached essentially the same conclusions (not shown). We also considered faster growing tumors. They showed essentially the same qualitative features but the time scale was shorter (not shown).

As it follows from the analysis above, even if the telomerase is inhibited, a tumor with significant replicative capacity could grow and in some cases can be large enough to lead to the patient's death. Thus, telomerase inhibition would be the best used in the context of adjuvant

where patients are treated to maintain a state of minimal residual disease. Other means (surgery, radiation, cytotoxics) are used to keep the tumor small while telomerase inhibitors would further limit the ability of tumor to expand locally or metastatically.

In tumors telomeres can be elongated, reduced or have equal length compared to the normal cell and there is a variability of telomere lengths between patients [10,21–25]. In some cases telomere length has negative correlation with telomerase activity [26]. Chemotherapy can reduce the level of telomerase in tumor cells but telomerase activity can be detected in tumor cells after surgery [27].

What is the condition for the use of anti-telomerase therapy? Let us denote by V_c the critical tumor volume that can lead to the patient's death and by V_0 and L_0 the initial tumor volume and initial telomere length, respectively. So, the number of doublings in the absence of the anti-telomerase therapy that are necessary to rich this critical volume can be calculated as $\ln(V_c/V_0)/\ln 2$. If telomerase is inhibited and inhibitor has no toxic effect (cell division is not suppressed) the maximal number of doublings can be calculated as $(L_0 - L_c)/l$, where L_c is the critical telomere length and l is the telomere shortening rate per cell division. Therefore, anti-telomerase therapy can be applied if

$$\ln(V_c/V_0)/\ln 2 > (L_0 - L_c)/l \tag{13}$$

and tumor cell population having large values of V_c, L_c, and l, and small values of V_0, L_0 is the best candidate for anti-telomerase therapy.

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